REMARKS

Introductory Comments:

Claims 7 and 27-31 were examined in the Office Action under reply and rejected under 35 U.S.C. §112, first and second paragraphs. These rejections are believed to be overcome by the above amendments and are otherwise traversed for reasons discussed below.

Overview of the Above Amendments and New Claims:

Claims 7, 29 and 31 have been amended to claim the subject invention with greater particularity. Claim 7 now recites that the method is for "inhibiting binding of the E2 protein of HCV to human cells" and that the CD81 protein comprises "amino acids 113-201 of the human CD81 amino acid sequence depicted in SEQ ID NO:21." Claim 29 has been amended to depend from claim 7 rather than from canceled claim 28 and for proper antecedent basis. Claim 31 has been amended to recite a sequence identifier. The specification has been amended to insert a sequence identification number.

Claims 27, 28 and 30 have been canceled and new claim 32 added which recites that the CD81 protein consists of the sequence of amino acids shown at positions 113-201 of the human CD81 amino acids sequence depicted in SEQ ID NO:21.

Support for the foregoing amendments may be found throughout the specification and claims as filed at, e.g., page 2, lines 27-29; page 8, lines 11-13; and Example 7, beginning at page 24.

The above amendments are made without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants reserve the right to pursue the canceled claims in a related application.

Formal Matters:

The Examiner requested a new Sequence Listing including the human CD81 sequence shown in Figure 1. A Sequence Listing as requested accompanies this response.

Rejection Under 35 U.S.C. §112, Second Paragraph:

Claim 7 was rejected under 35 U.S.C. §112, second paragraph as indefinite. The Office objects to the terminology "functional equivalent" in claim 7, arguing that despite the definition provided in the specification, the meaning of the term is unclear. Applicants disagree and continue to assert that the term is adequately defined in the specification. Nevertheless, in the interest of advancing prosecution, this phrase has been eliminated from the claims. Thus, this basis for rejection is believed to be overcome and withdrawal thereof is respectfully requested.

Rejection Based on Lack of Enablement:

Claims 7 and 27-31 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Office states:

> Claims 7 and 27-31 are drawn to the pharmaceutical use of a CD81 or functional equivalent thereof to reduce viral infectivity and encompasses human treatment using the protein or a functional equivalent. The specification does not teach that administration of a CD81 protein or any portion of a CD81 protein, or any compound that functions in the same way as CD81 insofar as it is capable of binding to HCV, in fact is of any therapeutic value to a human subject in reducing viral infectivity.

Office Action, page 4. However, applicants respectfully disagree with these contentions.

The Office cites *Hepatology* (1999) 29:990-992 ("Pileri")[1], stating that this reference "points out that merely blocking or preventing HCV E2-CD81 interaction may or may not be of therapeutic value." Office Action, page 4. However, the statement in Pileri that "[t]he therapeutic potential of this approach will depend on many unknowns" is made in the context of assays to screen for small molecules, modified nucleic acids and humanized antibodies that block the HCV E2-CD81 interaction. The present methods, on the other hand, depend on the use of a CD81 protein which retains the CD81 EC2 loop, the portion of CD81 which has been shown by applicants to bind to HCV E2. Example 6 of the application demonstrates that the EC2 loop of CD81 binds recombinant E2 and viral particles. Example 7 and Figure 11 of the application show that proteins containing the human EC2 loop of CD81 bound to E2 and inhibited binding of E2 to human cells.

Moreover, later reports confirm that CD81 binds to an HCV E1E2 heterodimer which is properly folded and interacts with conformation-dependent monoclonal antibodies. See, Lambot et al., *J. Biol. Chem.* (2002) 277:20625-20630, the abstract of which accompanies this response. Thus, CD81 has been shown to bind HCV using a molecule that retains the native conformation as found *in vivo*. Applicants submit that this is more than adequate evidence that the CD81 EC2 loop binds HCV.

The Action also cites Petracca et al., *J. Virol.* (2000) 74:4824-4830 ("Petracca"), stating that this reference illustrates that "mere knowledge of the association of CD81 and HCV is not sufficient to support predictability in treating HCV infection by administering a CD81 or a functional equivalent thereof." Office Action, page 4. However, to reiterate, Petracca actually supports applicants' statements regarding therapeutic efficacy. As reported in Petracca, CD81 is a cellular receptor for HCV and binds to HCV E2 with high affinity, analogous to the HIV gp120-CD4 interaction. It is of no consequence that internalization of ligands by CD81 is inefficient. In the present

[1]Applicants note that the authors on this citation were designated "Rice et al." by the Office but are actually Pileri et al.

methods, internalization is not necessary. All that is required is that HCV bind to the CD81 EC2 loop. This binding, in and of itself, leaves less circulating virus and therefore serves to decrease viral load. Eliminating or reducing the amount of circulating virus using a CD81 protein that binds circulating HCV, eliminates or reduces the amount of available virus for interacting with any cell surface receptor, including CD81. Thus, less HCV is internalized and hence less virus replicates.

The Office argues that the capacity to bind HCV *in vivo* cannot be extrapolated from the *in vitro* results because "HCV in an infected individual is likely to be complexed with antibodies and/or lipoproteins, and it is not known to what extent the existence of these complexes would be likely to affect the binding of CD81 to HCV." Office Action, page 5. However, this is pure speculation. It is highly unlikely that all circulating HCV would be complexed in such a way that the E2 region was unavailable for binding to administered CD81. Reducing viral load, whether or not the virus is completely eliminated, is useful in and of itself. For example, HCV viral load is known to be correlated with the development of heptocellular carcinoma. See, Ishikawa et al., *J. Gastroenterol. Hepatol.* (2001) 16:1274-1281, the abstract of which accompanies this response. Thus, even if all HCV is not available to bind administered CD81, a beneficial result can still be obtained.

The Office also states "HCV E2 comprises a hypervariable region, and it is not apparent that all variant HCV E2's would be expected to retain the capability to bind a CD81 protein." However, there is no requirement that applicants demonstrate that all HCV variants be bound. Applicants are not required to show unerring efficacy in order to comply with the requirements of 35 U.S.C. §112, first paragraph. As stated by the court in *In re Sarett*, 140 USPQ 474, 486 (CCPA 1964):

> [T]he mere *possibility* of inclusion of inoperative substances does not prevent *allowance* of broad claims. ... If they are so broad as to be vulnerable, no one but the patentee will suffer from it.

> It is certainly not incumbent on an applicant who has made a broad process invention and supported it by an adequately broad disclosure to demonstrate the operativeness of every substance falling within the scope of the broad claims to which he is entitled. ... The function of the claims is to *point out* the invention and *define* the scope of the monopoly, not to exclude substances which are possibly of no use in practicing the invention.

Thus, the fact that the claims may read on inoperative embodiments cannot be used as a proper basis for rejecting the claims under 35 U.S.C. §112, first paragraph.

In making the present rejection, then, it appears the Patent Office is attempting to impose a requirement upon applicants not only to show how to make and use the claimed compositions, but also to establish an unerring *degree of effectiveness* of such formulations. This requirement far exceeds applicants' statutory obligations under §112. These are the kinds of questions that the Food and Drug Administration--the agency Congress has created to administrate safety and efficacy standards in pharmaceutical formulations intended for human applications--is intended to address. These are not the kinds of questions which the Patent Office should be asking in assessing enablement under 35 U.S.C. §112. See, e.g., *In re Brana*, 34 USPQ 1436 (Fed. Cir. 1995) and the Examiner Guidelines for Biotech Applications, 60 Fed. Reg. 97 (1995). Accordingly, applicants submit that this rejection is improper and should be withdrawn.

For all of the foregoing reasons, then, applicants submit that the present claims are fully enabled. Reconsideration and withdrawal of all rejections under 35 U.S.C. §112, first paragraph, is thus respectfully requested.

CONCLUSION

Applicants respectfully submit that the claims are novel and nonobvious over the art and comply with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

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Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 7, 29 and 31 have been amended as follows:

7. (Twice amended) A method for [treating an infection] inhibiting binding of the E2 protein of HCV to human cells comprising administering to a patient infected with HCV [a therapeutically] an amount of a CD81 protein effective to bind HCV[amount of a CD81 protein, or a functional equivalent thereof, reduce the infectivity of the virus], wherein the CD81 protein comprises amino acids 113-201 of the human CD81 amino acid sequence depicted in SEQ ID NO:21.

29. (Amended) The method of claim [28] 7, wherein the human CD81 protein is a soluble form of the CD81 protein that comprises a deletion of one or more of the transmembrane binding domains depicted as TM1, TM2, TM3 and TM4 in Figure 1.

31. (Amended) The method of claim 7, wherein the CD81 protein comprises the human CD81 amino acid sequence depicted in [Figure 1] SEQ ID NO:21.

Claims 27, 28 and 30 have been canceled.

New claim 32 has been added:

--32. (New) The method of claim 7, wherein the CD81 protein consists of the sequence of amino acids shown at positions 113-201 of the human CD81 amino acid sequence depicted in SEQ ID NO:21.--

In the Specification:

The paragraph beginning at page 13, line 11 has been amended as follows:

Figure 1 is a sequence alignment showing the homology between human (SEQ ID NO:21), chimpanzee (SEQ ID NO:16), green monkey (SEQ ID NO:17), hamster (SEQ ID NO:18), rat (SEQ ID NO:19) and mouse (SEQ ID NO:20) CD81 gene sequences.